REMARKS

The issues outstanding the Office Action mailed May 4, 2007, are the rejections under 35 U.S.C. §101, §112, §103 and obviousness-type double patenting. Reconsideration of these issues, in view of the following discussion, is respectfully requested.

Foreign Priority

It is argued, at page 2 of the Office Action, that the benefit of priority is denied as there is no "certified translation" of the priority document. In fact, such a certified translation is unnecessary. See 35 U.S.C. §119(b). Note also MPEP §201.14. All that is required is a certified copy of the foreign language priority document. Such a certified copy has been received herein (please see the filing receipt of the present application). Thus, the priority claim in the present application is correctly made, and priority ***must*** be accorded. The same is respectfully requested.

Rejection under 35 U.S.C. §101

Claim 14 has been rejected under 35 U.S.C. §101. Reconsideration thereof is respectfully requested, in view of reformatting of the "use" claims into a method claim for U.S. practice. It is submitted that the rejection is moot, and withdrawal thereof if respectfully requested.

Rejections under 35 U.S.C. §112

Claims 3-14 have been rejected under 35 U.S.C. §112, second paragraph. Reconsideration thereof is respectfully requested.

Claim 14

As noted above in connection with the rejection under 35 U.S.C. §101, claim 14 has been reformatted for U.S. practices in method claims. Accordingly, the claim is not indefinite and withdrawal of this portion of the rejection is respectfully requested.

Claims 3-12

Claims 3-12 have been rejected under 35 U.S.C. §112, second paragraph, as the result of the terms "salifying" and "acidifying." With respect to the term "salifying", claim 3 has been amended in order to indicate that forming of a carboxylic acid salt occurs, although it is submitted that "salifying", i.e., a production of a salt, is a term well known in the art. Similarly, "acidifying", e.g., by adding an acid to the solution, is also a well-understood term of art. Inasmuch as the term "acidifying" is manifestly unambiguous to one of ordinary skill in the art, it is not seen that further amendment is necessary. Moreover, with respect to the comment on page 3 of the Office Action, that there are no reaction steps in acidifying, it is submitted that "acidifying", a verb, is a reaction step. Withdrawal of the rejection is respectfully requested.

With respect to claim 13, it is submitted that the expression "pharmaceutical composition", per se, excludes toxic doses. However, inasmuch as the amendment does not change the scope of the claim either literally, or for purposes of the doctrine of equivalents, a minor clarification has been made. Withdrawal of this rejection is thus also respectfully requested.

Rejections under 35 U.S.C. §102

Claims 1-2 and 13 have been rejected under 35 U.S.C. §102(b). Reconsideration thereof is respectfully requested.

It is argued at page 4 of the Office Action, that Brunet (WO '113), commonly assigned with the present application, discloses the presently claimed compounds. It is thus believed evident that the examiner is overlooking the present claim recitation that the compound is a "metastable form." In order to clarify this, claim 2 has been combined with claim 1. Claim 2 recites characteristics which are particular to the metastable form of the compound. It is clear that the metastable form, defined by its x-ray diffraction spectrum, is a distinct species from that disclosed in Brunet, e.g., defined by its spectrum (see example

16(b) at col. 36, page 50), as the "stable" form. Thus, the present claims are clearly novel over Brunet, and withdrawal of the anticipation rejection is respectfully requested.

Claims 1-2 and 13 have also been rejected under 35 U.S.C. §102(e) over Brunet '758. The '758 application is equivalent to the WO '113, and, for the reasons discussed above, also does not anticipate the present claims. Withdrawal of this rejection is therefore also respectfully requested.

Obviousness-Type Double Patenting

Claims 1-2 and 13 have also been rejected under the doctrine of Obviousness-Type Double Patenting over claims 1-8 and 18-19 of Brunet. As noted above, Brunet discloses the stable form of the compounds as disclosed by the spectrum therein. It is respectfully submitted that Brunet does not suggest the metastable form, nor does Brunet disclose a method for its production. Attention is directed to the attached internal memorandum, discussing differences between the stable and metastable forms. Moreover, the present specification, for example, at page 13 in example 3, discusses the advantages of metastable form of the compounds over the stable form. It is shown, in this example, that the metastable form exhibits significant advantage in a pharmaceutical context, by allowing production of an active agent with greater specific surface area and greater density than the stable form of the compound. A greater density, as discussed in example 3, provides significant advantage in formulation of pharmaceuticals, inasmuch as it enables achieving a higher dosage with a smaller amount of active material.

Since a cornerstone of *obviousness*-type double patenting is that the claims of the cited reference must render the application claims *obvious*, it is evident that this unexpected advantage clearly rebuts any presumption of obviousness which may exist. Accordingly, it is submitted that the claims of Brunet *do not* suggest the present claims in their metastable form, and that the obviousness-type double patenting rejection should be withdrawn.

The claims in the application are submitted to be in condition for allowance. However, if the examiner has any questions or comments, he is cordially invited to telephone the undersigned at the number below.

No fee is believed due with this response, however, the Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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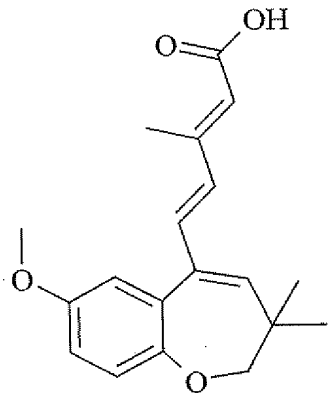
Attorney Docket No.: MERCK-2992

Date: August 6, 2007

HBS/cak

Investigation of polymorphic/pseudopolymorphic behaviour of LM 4156

1. Formula



2. Summery

LM 4156 shows a polymorphic behaviour. Two polymorphs and the glassy state were found.

All crystal forms are characterized using differential scanning calorimetry (DSC), thermogravimetry (TGA), infrared spectroscopy (IR), and x-ray powder diffraction (XRD) for analysis. The following table summarizes the physicochemical properties of the different forms.

form	*stoichiometry*	*mp.*	*$\Delta_f H$ (kJ/mol)*	*Remarks*
A	*X*	*154°C - 156°C*	*38.4*	
B	*X*	*151°C - 153°C*	*35.4*	
glass	*X*	-	-	*T_g 42°C, T_{cc} 110°C*

X = LM 4156

The polymorphs A and B are monotropically related. Form A is the thermodynamically stable one at all temperatures. Form B is metastable.

The glassy state should be not stable during storage at room temperature by reason of the low glass transition temperature.

LM 4156 shows no tendency to formation of hydrates or solvates.

3. Results

A) Form A

Fig. 1 shows a DSC measurement of form A from room temperature to 180°C. The melting point was determined at 156°C. The melting enthalpy is $\Delta_f H$ = 38.4 kJ/mol. The observed melting point is independent of the DSC heating rate. The compound is thermal stable during melting. A partly decomposition doesn't take place. No further thermal effect was detected below the melting point. The crystal form doesn't contain bound solvents. Thermogravimetric measurements have shown only low solvent residues from the different preparations (see chapter D). Form A is nonhygroscopic. During one-week storage at different levels of relative humidity no significant amount of water is taken up (fig. 2). The IR and XRD spectra are shown in appendices A and B.

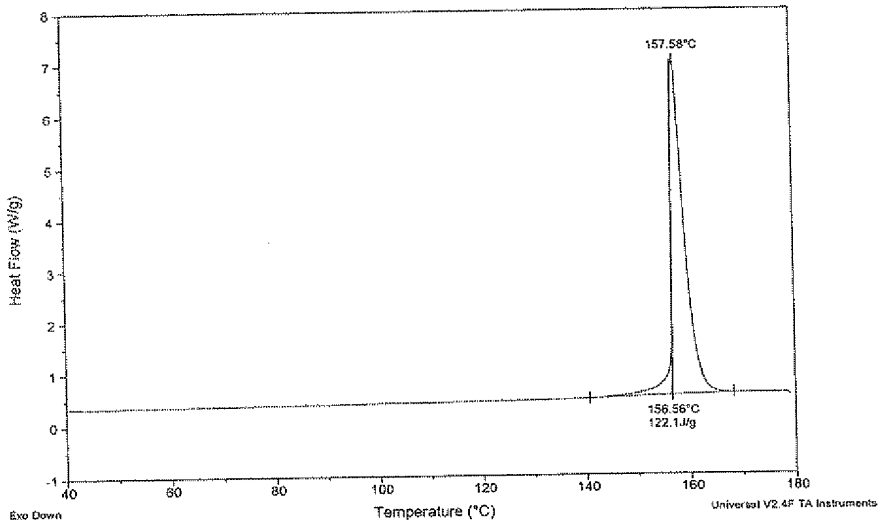


Figure 1 DSC measurement of form A (hermetic Al pan with 200 µm pinhole, β = 10 K/min)

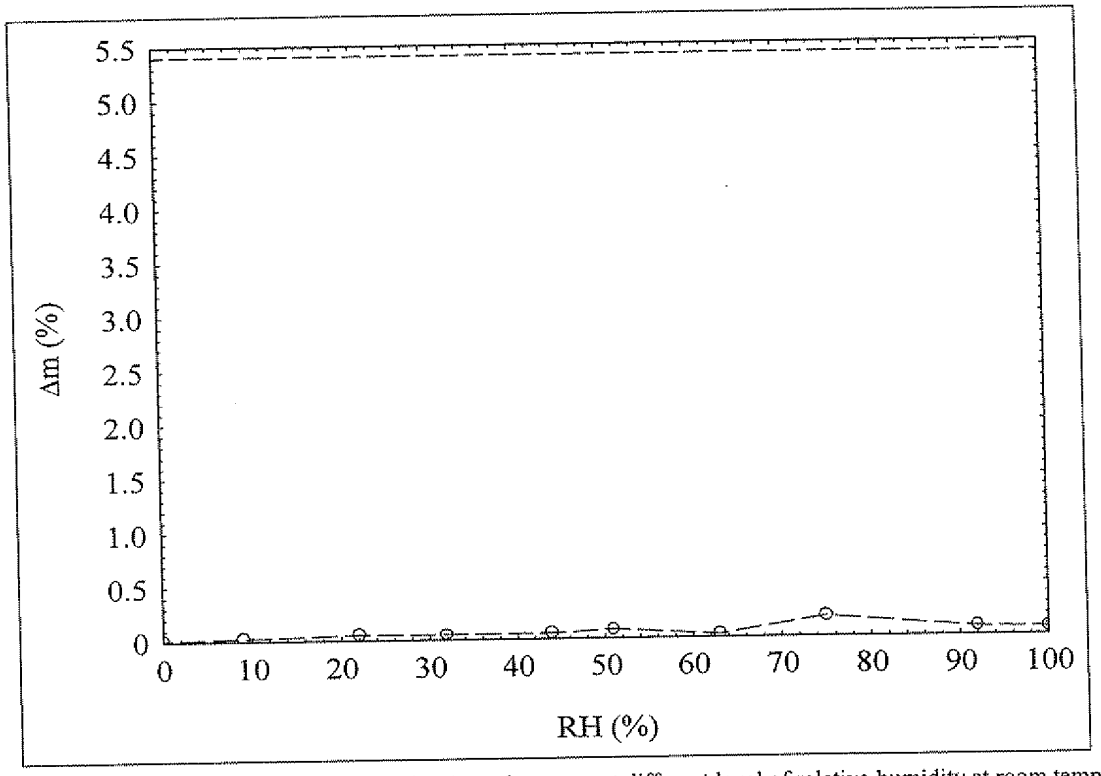


Figure 2 Hygroscopicity function of form A after 1-week storage at different level of relative humidity at room temperature (sample contains 1.7 % ethyl acetate, determination of water content by means of TGA)

B) Form B

Form B melts at 151°C-153°C (fig. 3). The melt of B is able to crystallize partly to form A (fig 4). The degree of recrystallization is influenced by the DSC heating rate. The lower the heating rate the higher the part of recrystallized form A is. The melting enthalpy of form B is $\Delta_f H$ = 35.4 kJ/mol. Form B is also nonhygroscopic. During one-week storage at different levels of relative humidity no significant amount of water is taken up (fig. 5). The IR and XRD spectra are shown in appendices A and B.

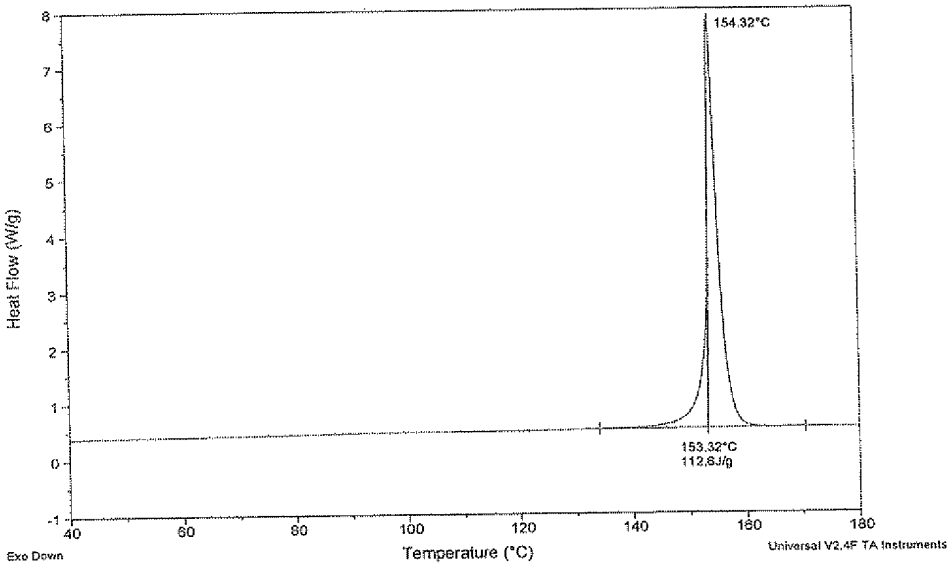


Figure 3 DSC measurement of form B (hermetic Al pan, β = 10 K/min)

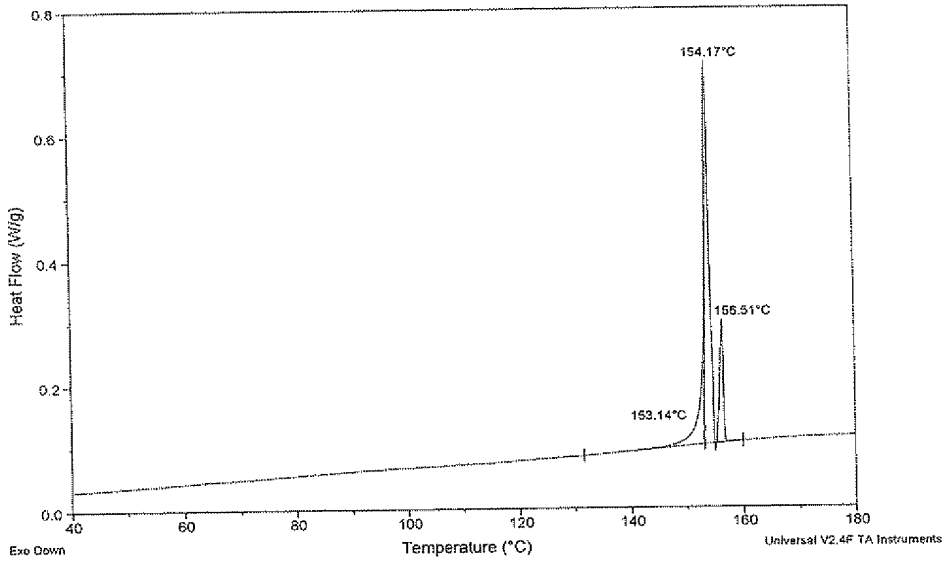


Figure 4 DSC measurement of form B (hermetic Al pan, β = 0.5 K/min)

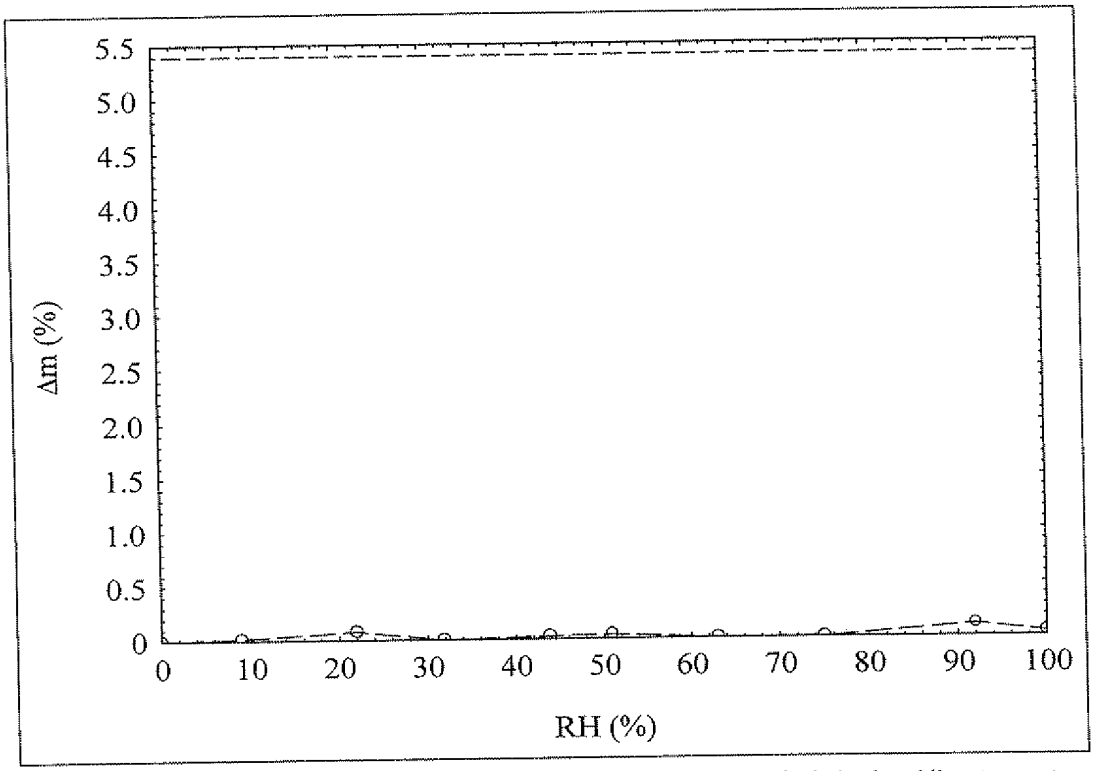


Figure 5 Hygroscopicity function of form B after 1-week storage at different level of relative humidity at room temperature (determination of water content by means of TGA)

C) Glassy state (amorphous form)

The glassy state results from a solidification of a melt. Fig. 6 shows a typical DSC measurement of an amorphous state. The glass transition temperature is detected approximately at 40°C. That means that the glassy state should be not stable during storage at room temperature. The use of amorphous LM 4156 in formulations (possibly yielded by lyophilization or spray drying) is unsuitable. Above 100°C a cold crystallization to a crystalline form takes place. The melting point at 153°C indicates that form B is yielded. IR and XRD measurements on amorphous samples heated above the cold crystallization temperatures confirm this. During the melting of form B a partial recrystallization to form A takes place.

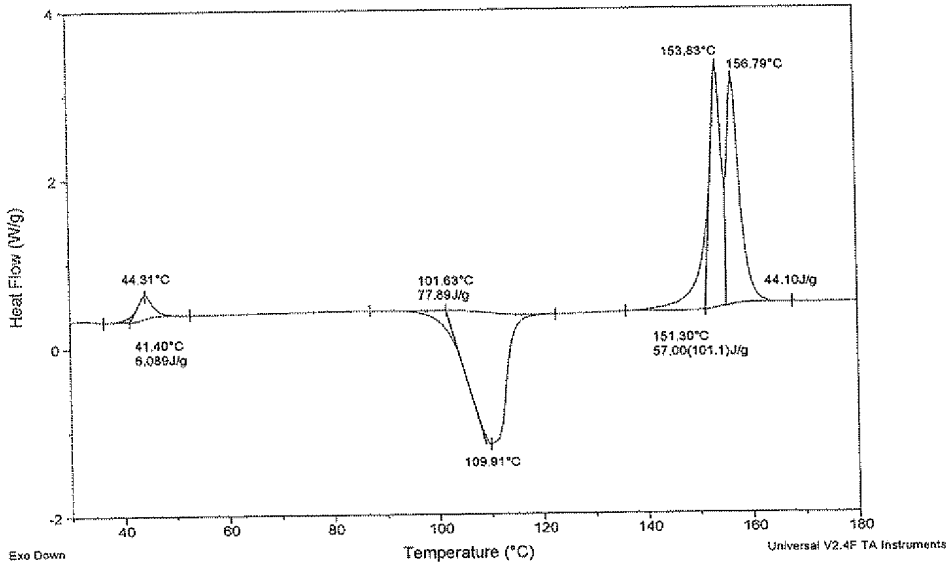


Figure 6 DSC measurement of the amorphous form (hermetic Al pan with 200 µm pinhole, β = 10 K/min)

D) Crystallization and recrystallization

A crystallization and recrystallization screening procedure is carried out with LM 4156. In all cases form B was the starting material (the solvent free material). The tables 1 and 2 give the results.

Table 1 Crystallization at room temperature (solvent evaporation)

solvent	DSC result	IR result	remarks	solvent residue (TG)
water	B	B	1)	0.35 %
methanol	A	A	2)	1.09 %
ethanol	A	A	2)	2.58 %
2-propanol	A (+ B)	A	2), 3)	1.93 %
ethyl acetate	A (+ B)	A	2), 3)	4.19 %
tetrahydrofuran	A	A	2)	1.36 %
acetonitrile	A	A	2)	1.45 %
acetone	A	A	2)	2.32 %
toluene	B	B	2)	1.99 %
n-heptane	B	B	1)	1.04 %

1) suspension
2) solution
3) DSC measurement indicates a small part of B

Table 2 Recrystallization (maximum temperature approximately 50°C)

solvent	DSC result	IR result	remarks	solvent residue (TG)
water	B	B	1), 60°C	0.05 %
methanol	A	A	2)	0.76 %

ethanol	(B)	A	2), 3)	1.86 %
2-propanol	B	A + B	2), 4)	2.32 %
ethyl acetate	(B)	A	2), 3)	3.96 %
tetrahydrofuran	(B)	A	2), 3)	2.44 %
acetonitrile	A	A	2)	1.87 %
acetone	(B)	A	2), 3)	3.22 %
toluene	B	B	2)	2.85 %
n-heptane	B	A + B	1), 4), 60°C	1.88 %

1) suspension
2) solution
3) DSC measurements give a broad melting signal
3) a differentiation of form B and a mixture of A and B by DSC is difficult

Temperature and solvent effects influence the formation of both polymorphs. In the most cases at room temperature form A resulted from the crystallizations. Recrystallisations at higher temperatures gave partly form B. This behaviour indicates that form A is more stable at room temperature.

Additionally all samples were investigated by thermogravimetry. The samples contain solvent residues. CRE 17815 doesn't tend to formation of hydrates or solvates.

E) Stability relationship

According to the Burger's heat-of-fusion rule or entropy-of-fusion rule there are a monotropic relationship between the polymorphs A and B. Table 3 summarizes the thermodynamic characteristics of both forms.

Table 3

polymorph	T_f (°C)	T_f (K)	$\Delta_f H$ (kJ/mol)	$\Delta_f S$ (J/molK)
A	156	429.15	38.4	89.5
B	153	426.15	35.4	83.0

The higher melting polymorph has the higher heat of fusion and the higher entropy of fusion. A monotropic system sometimes contains an additional exothermal phase transition. The solid-solid phase transition is influenced by the kinetics of the change from the metastable form to the stable form. If two melting points are observed the solid-solid phase change is kinetically hindered. An approximation of the Gibb's functions of both forms gives two lines without an intersection point below the melting points.

$$\Delta G = \Delta H - T\Delta S$$

The point of intersection of both functions above the melting points corresponds to a theoretical transition point. Fig. 7 shows this approximation for LM 4156. A theoretical transition point at 188°C results. Polymorph A is the thermodynamically stable form at any temperature. Polymorph B is metastable.

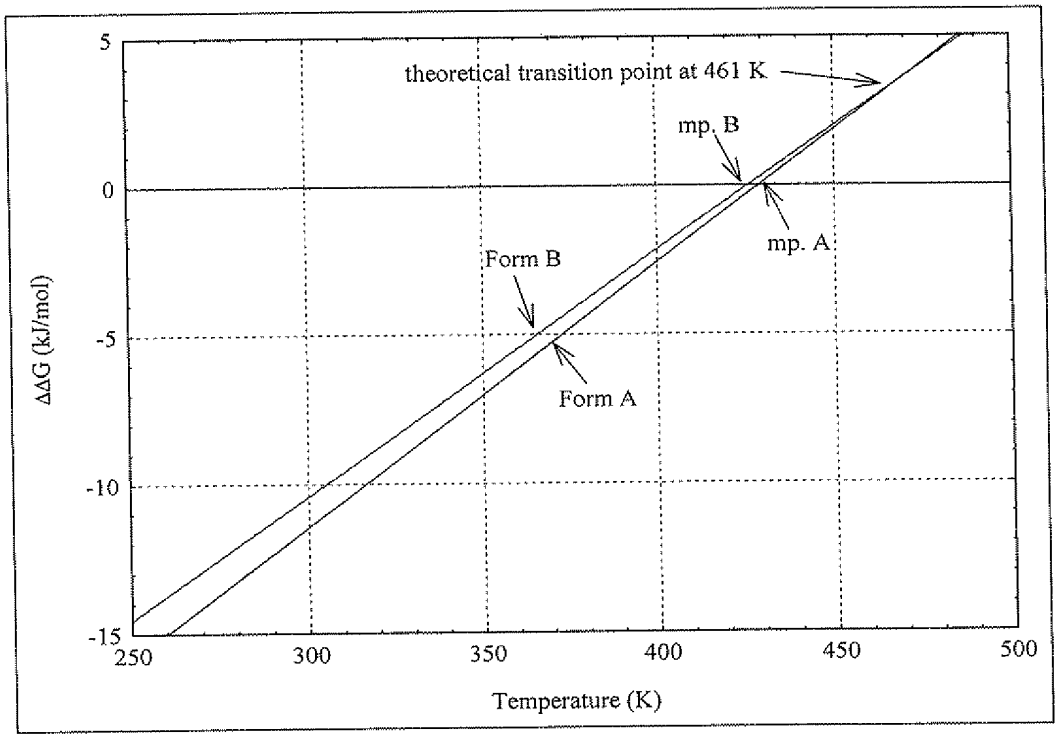
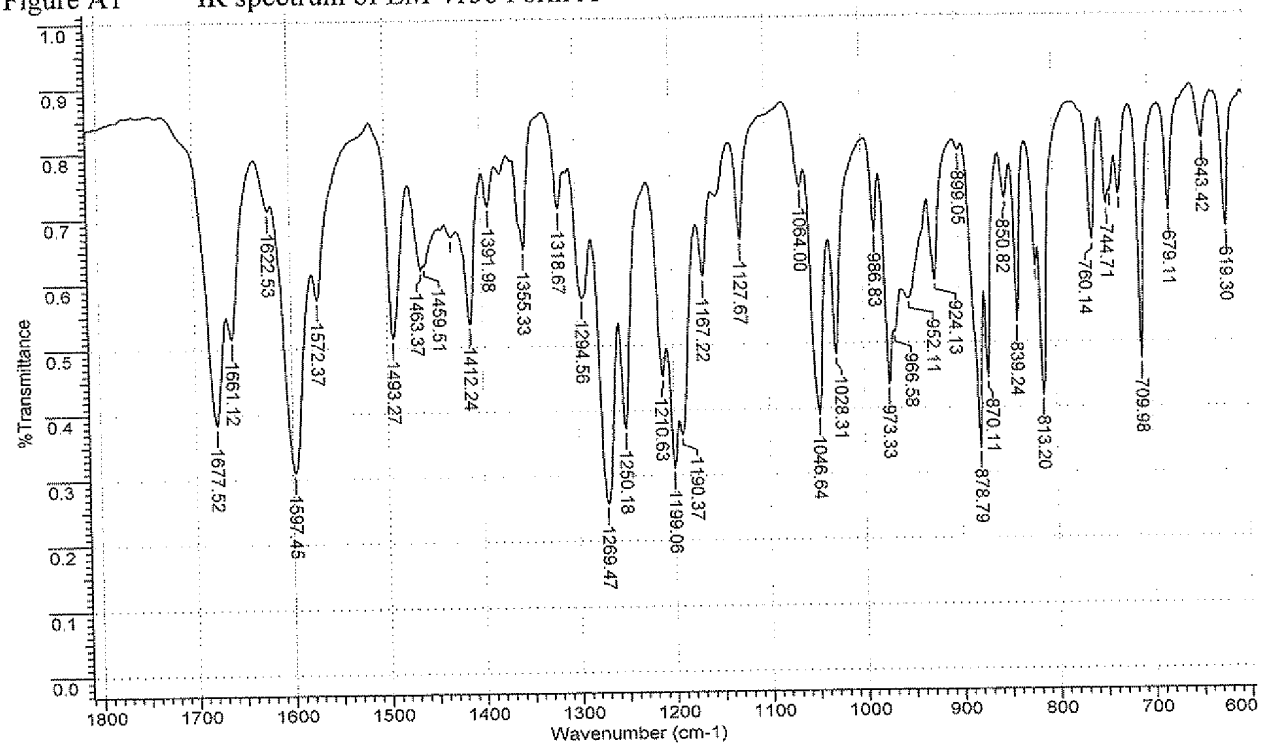


Figure 7 Calculation of Gibbs functions of both forms

Appendix A – IR spectra

Figure A1 IR spectrum of LM 4156 Form A



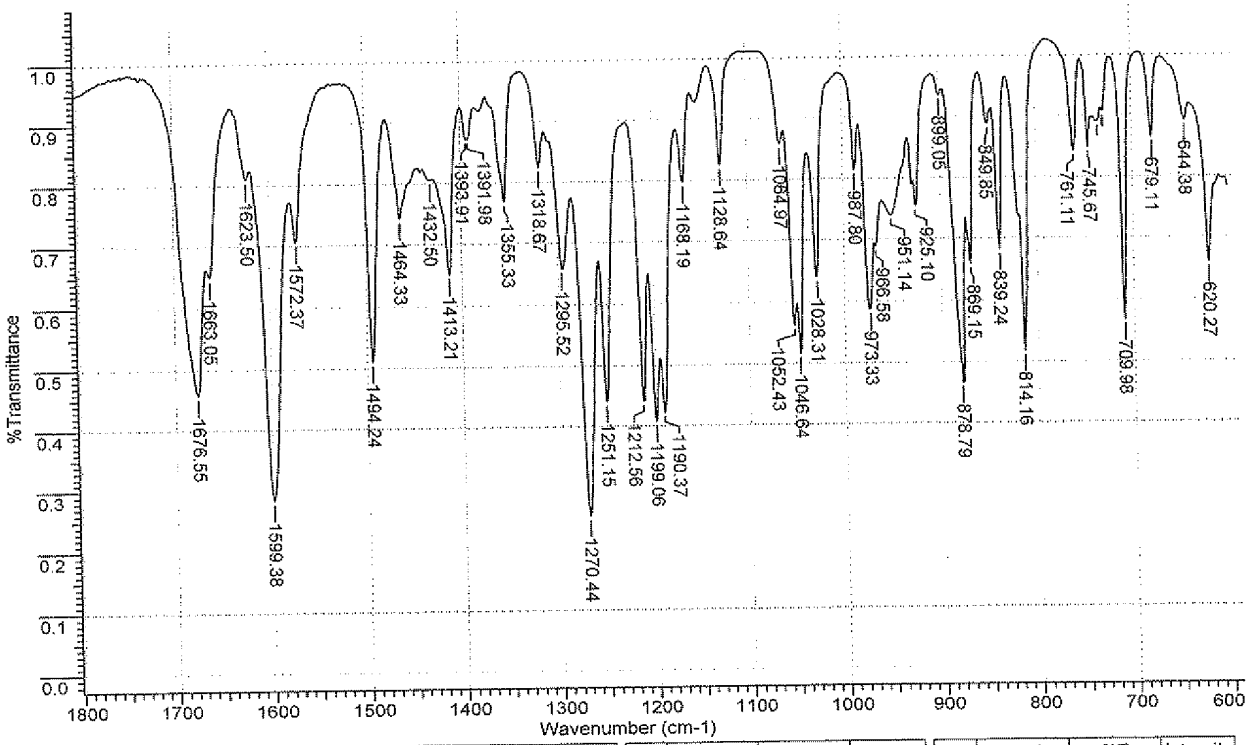
No	cm-1	%T	Intensity
1	619.30	0.674	M
2	643.42	0.810	M
3	679.11	0.699	M
4	709.98	0.473	S
5	731.20	0.725	M
6	740.85	0.729	M
7	744.71	0.709	M
8	760.14	0.655	M
9	813.20	0.418	S
10	819.95	0.616	S
11	839.24	0.532	S
12	850.82	0.720	M
13	870.11	0.445	S

No	cm-1	%T	Intensity
14	878.79	0.337	VS
15	899.05	0.794	M
16	924.13	0.596	S
17	952.11	0.567	S
18	966.58	0.516	S
19	973.33	0.436	S
20	986.83	0.670	M
21	1028.31	0.482	S
22	1046.64	0.391	S
23	1064.00	0.740	M
24	1127.67	0.660	M
25	1167.22	0.604	S
26	1190.37	0.362	S

No	cm-1	%T	Intensity
27	1199.06	0.311	VS
28	1210.63	0.452	S
29	1250.18	0.373	S
30	1269.47	0.257	VS
31	1294.56	0.573	S
32	1318.67	0.710	M
33	1355.33	0.648	S
34	1391.98	0.715	M
35	1412.24	0.534	S
36	1431.53	0.668	M
37	1459.51	0.624	S
38	1463.37	0.618	S
39	1493.27	0.514	S

No	cm-1	%T	Intensity
40	1572.37	0.574	S
41	1597.45	0.310	VS
42	1622.53	0.711	M
43	1661.12	0.515	S
44	1677.52	0.383	S
45	2837.99	0.689	M
46	2870.79	0.675	M
47	2932.52	0.643	S
48	2959.53	0.652	S
49	3008.73	0.715	M
50	3015.48	0.714	M

Figure A2 IR spectrum of LM 4156 Form B



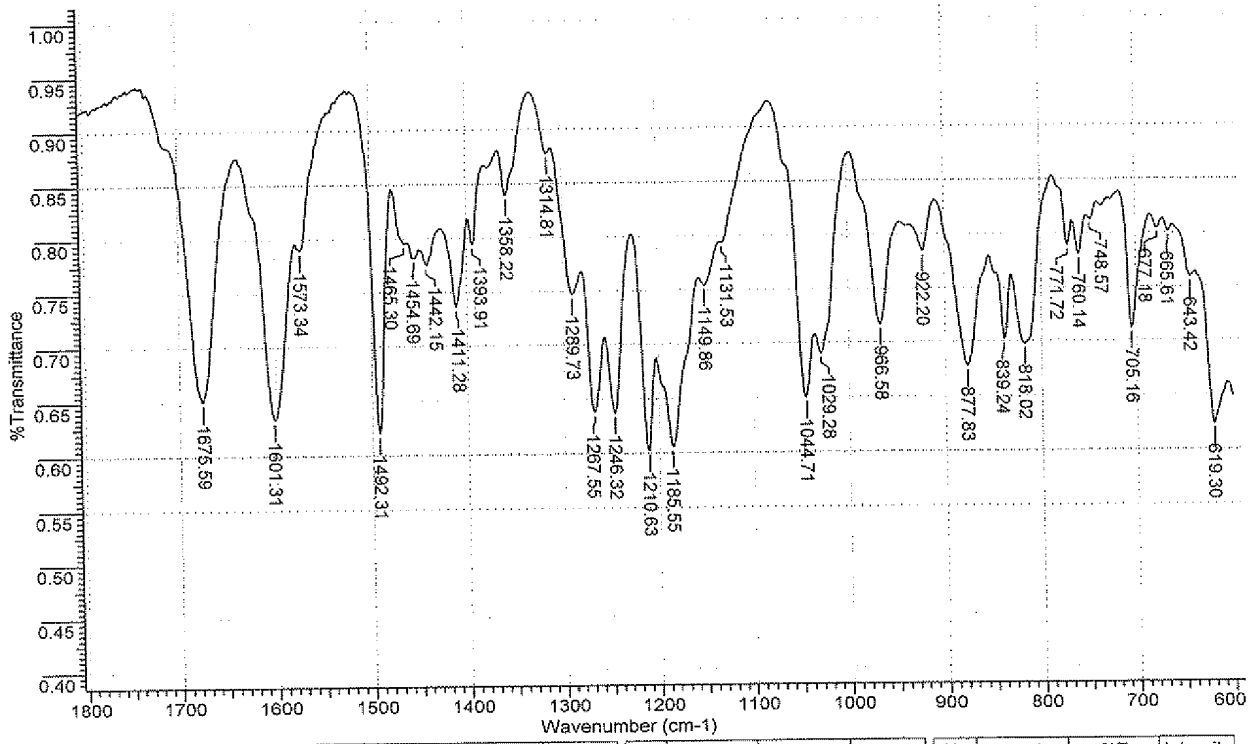
No	cm-1	%T	Intensity
1	620.27	0.660	M
2	644.38	0.892	W
3	679.11	0.865	W
4	709.98	0.568	M
5	730.24	0.907	W
6	736.03	0.891	W
7	745.67	0.849	W
8	761.11	0.843	W
9	814.16	0.518	M
10	839.24	0.683	M
11	849.85	0.889	W
12	869.15	0.660	M
13	878.79	0.466	S

No	cm-1	%T	Intensity
14	899.05	0.936	W
15	925.10	0.755	M
16	951.14	0.740	M
17	966.58	0.688	M
18	973.33	0.587	M
19	987.80	0.815	W
20	1028.31	0.641	M
21	1046.64	0.517	M
22	1052.43	0.562	M
23	1064.97	0.859	W
24	1128.64	0.825	W
25	1168.19	0.797	W
26	1190.37	0.422	S

No	cm-1	%T	Intensity
27	1199.06	0.408	S
28	1212.56	0.441	S
29	1251.15	0.442	S
30	1270.44	0.254	S
31	1295.52	0.659	M
32	1318.67	0.825	W
33	1355.33	0.769	W
34	1391.98	0.872	W
35	1393.91	0.872	W
36	1413.21	0.651	M
37	1432.50	0.806	W
38	1464.33	0.743	M
39	1494.24	0.511	M

No	cm-1	%T	Intensity
40	1572.37	0.707	M
41	1599.38	0.284	S
42	1623.50	0.810	W
43	1663.05	0.650	M
44	1676.55	0.458	S
45	2837.99	0.863	W
46	2871.75	0.847	W
47	2934.45	0.819	W
48	2960.50	0.818	W
49	3018.38	0.898	W

Figure A3 IR spectrum of LM 4156 glassy state



No	cm-1	%T	Intensity
1	619.30	0.624	M
2	643.42	0.759	W
3	665.61	0.802	W
4	677.18	0.804	W
5	705.16	0.712	M
6	748.57	0.813	W
7	760.14	0.781	W
8	771.72	0.789	W
9	818.02	0.698	M
10	839.24	0.702	M

No	cm-1	%T	Intensity
11	877.83	0.678	M
12	922.20	0.764	W
13	966.58	0.717	M
14	1029.28	0.691	M
15	1044.71	0.650	M
16	1131.53	0.794	W
17	1149.86	0.754	W
18	1185.55	0.606	M
19	1210.63	0.603	M
20	1246.32	0.637	M

No	cm-1	%T	Intensity
21	1267.55	0.638	M
22	1289.73	0.748	W
23	1314.81	0.878	W
24	1358.22	0.840	W
25	1393.91	0.794	W
26	1411.28	0.737	W
27	1442.15	0.775	W
28	1454.69	0.782	W
29	1465.30	0.795	W
30	1492.31	0.621	M

No	cm-1	%T	Intensity
31	1573.34	0.790	W
32	1601.31	0.634	M
33	1675.59	0.650	M
34	2834.13	0.838	W
35	2869.82	0.825	W
36	2905.51	0.829	W
37	2954.71	0.804	W

Appendix B – XRD spectra

Figure B1 XRD spectrum of LM 4156 form A

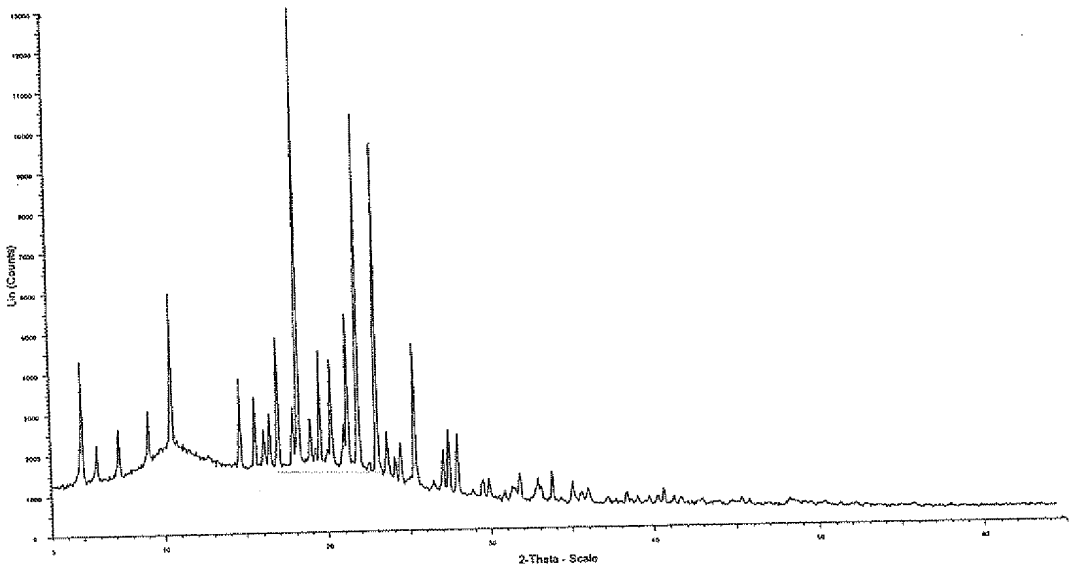


Figure B2 XRD spectrum of LM 4156 form B